JACC Vol. 12, No. 2
August 1988:289–300

CLINICAL STUDIES

Early Recovery of Left Ventricular Function After Thrombolytic Therapy for Acute Myocardial Infarction: An Important Determinant of Survival

FLORENCE H. SHEEHAN, MD, ROLF DOERR, MD,* WOLFGANG G. SCHMIDT, MD,*
EDWARD L. BOLSON, MS, RAINER UEBIS, MD,* RAINER von ESSEN, MD,*
SVEN EFFERT, MD,* HAROLD T. DODGE, MD, FACC

Seattle, Washington and Aachen, West Germany

Thrombolytic therapy for acute myocardial infarction reduces early mortality, but full recovery of left ventricular function after reperfusion is delayed. Therefore, the relations among reperfusion, survival and the time course of left ventricular functional recovery were examined in 226 patients treated with intracoronary streptokinase; 77% (134 patients) had sustained reperfusion and 31 patients had no reperfusion or had reocclusion by day 3. Wall motion was measured from contrast ventriculograms performed in the acute period and 3 days later in the central and peripheral infarct regions and the noninfarct region by the centerline method in 165 patients.

Patients with reperfusion had better survival ($p < 0.05$, mean follow-up 4.5 years) and a higher ejection fraction at 3 days (52 ± 12 versus 46 ± 10%, $p < 0.02$) attributable to a significantly different change in peripheral infarct region function between the acute and 3 day studies (0.1 ± 1.0 versus −0.3 ± 0.9 SD, $p < 0.05$). These early functional changes were significant in patients with anterior myocardial infarction and showed similar trends in those with inferior myocardial infarction. On Cox regression analysis, function measured at 3 days was more predictive of survival than was function measured acutely (chi square for acute ejection fraction = 11.48 versus 24.59 at 3 days).

Although, as previously reported, >45% of total recovery of left ventricular function occurs later, the ejection fraction achieved by day 3 is already predictive of survival. Thus, the mechanism by which successful thrombolytic therapy enhances survival is improvement of regional and global left ventricular function early after acute myocardial infarction.

(J Am Coll Cardiol 1988;12:289–300)

The hypothesis underlying thrombolytic therapy for acute myocardial infarction is that reperfusion will salvage myocardium and thereby enhance survival. To date there are abundant experimental and clinical data documenting the efficacy of thrombolytic therapy in achieving reperfusion, the effect of reperfusion in salvaging left ventricular function and the effect of thrombolytic therapy in enhancing survival. However, a clear relation between myocardial salvage and survival in humans has not yet been demonstrated (1). In the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto (GISSI) trial (2) and Western Washington (3,4) intracoronary streptokinase trial, streptokinase-treated patients had enhanced survival, but left ventricular function was not measured or did not differ between treated and control patients. In the Western Washington intravenous streptokinase trial (5) and in the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) trial from the Federal Republic of Germany (6), treatment with streptokinase benefitted left ventricular function. However, the trend toward improved survival did not reach statistical significance because the number of patients was too small or the mortality in the control group was too low. In the Netherlands (7,8) and New Zealand (9) trials, streptokinase therapy significantly enhanced both survival and left ventricular function, suggesting a relation between salvage and survival.

Examination of survival curves from the Western Washington (10), GISSI (2) and Netherlands (7) trials shows that

From the Cardiovascular Research and Training Center, University of Washington, Seattle, Washington and *Department of Internal Medicine I, Rheinisch-Westfaelische Technische Hochschule (RWTH), Aachen, West Germany. This study was supported in part by grants from the R.J. Reynolds Foundation, Winston-Salem, North Carolina and Grants HL-27819 and HL-19451 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland.

Manuscript received December 21, 1987; revised manuscript received February 24, 1988, accepted March 17, 1988.

Address for reprints: Florence H. Sheehan, MD, University of Washington, RG-22, Seattle, Washington 98195.

0735-1097/88/$3.50

JACC Vol. 12, No. 2
August 1988:289-300

the benefit from thrombolytic therapy occurs early after acute myocardial infarction. After hospital discharge, the difference in survival between treated and control patients may remain but does not further increase. Thus, thrombolysis reduces mortality in the first few days after acute myocardial infarction, the period when most deaths take place (11). Therefore, the present study was performed to assess early recovery of left ventricular function after thrombolytic therapy and its correlation with survival in patients with acute myocardial infarction.

Study patients. Patients were enrolled in the study between May 1980 and May 1984 if they had chest pain suggestive of acute myocardial infarction lasting >30 min, ST segment elevation ≥0.2 mV in electrocardiographic (ECG) leads II, III or aVF or ≥0.3 mV in the precordial leads and no contraindications to streptokinase therapy, and if thrombolytic therapy could be initiated ≤8 h after onset of chest pain. No elderly patients were excluded solely on the basis of age. After pretreatment with 250 mg methylprednisolone, 10,000 U heparin and 1 g aspirin, coronary arteriography was performed and streptokinase was administered by the intracoronary route into the thrombosed vessel at 3,000 U/min until 30 min after reperfusion occurred or for a maximal period of 90 min if reperfusion was not achieved. Contrast ventriculography was then performed in the 30° right anterior oblique projection. Among the patients who had reperfusion in the acute period (≤90 min after the start of streptokinase infusion), those with single vessel disease were considered to be candidates for immediate angioplasty to reduce the residual stenosis, and those with multivessel disease underwent coronary artery bypass surgery during the acute hospitalization if reperfusion occurred <4 h after symptom onset. If reperfusion was not achieved by streptokinase, mechanical revasculation was attempted with angioplasty.

The catheter sheath was left in place at the conclusion of the acute catheterization, and the patient was transferred to the coronary care unit and treated with intravenous heparin at 25,000 to 30,000 U/24 h and nitroglycerin at 2 to 4 μg/min for 3 days. Coronary arteriography and left ventriculography were then repeated, and the sheath was removed. All patients were subsequently continued on anticoagulant therapy with phenprocoumon or aspirin for 6 months. They were then rehospitalized for a third cardiac catheterization.

To reduce the number of variables affecting the measurement of left ventricular function and the effect of streptokinase on its recovery, only patients with total occlusion of either the left anterior descending or right coronary artery were selected. In addition, only patients whose acute ventriculograms could be analyzed and in whom the perfusion status of the infarct-related artery was known 3 days after myocardial infarction were included. The resulting study group comprised 226 (57%) of the 395 patients enrolled and treated during this period. Ventriculography was not incorporated into the 3 day catheterization protocol until after the first 50 patients were treated. Thus, 165 of the 226 patients had analyzable contrast ventriculograms from both the immediate and 3 day postinfarct catheterizations.

Analysis of coronary and ventricular angiograms. Coronary angiograms were visually assessed by two observers. Reperfusion was defined as complete opacification of the infarct-related artery after streptokinase therapy or angioplasty in the acute period. Patients were considered to have sustained reperfusion if the infarct artery was still patent at 3 days. The artery was considered reoccluded if reperfusion was achieved acutely but either the artery was nonpatent at 3 days or clinical reinfarction at the same site as the original myocardial infarction occurred before the 3 day angiogram was obtained.

The endocardial contours of the left ventricle at end-diastole and end-systole were either traced by author W.G.S. or traced by another observer and reviewed by W.G.S. Only nonpostectopic normal sinus beats were analyzed. In difficult cases, authors F.H.S. and W.G.S. interpreted the images together. The contours were digitized and the x, y coordinates were transmitted by way of the BITNET satellite communications network to Seattle for analysis. Left ventricular volume was calculated with the area-length method (12) and used to determine the ejection fraction. Regional wall motion was calculated with the centerline method (13), which calculates motion along 100 chords drawn perpendicular to a centerline constructed midway between the end-diastolic and end-systolic contours and expresses abnormality in units of standard deviation (SD) from the normal mean. Hypokinesia in the central infarct region was calculated as the mean motion of chords lying in the 50% of the infarct artery territory whose motion was most depressed compared with normal motion (14). In addition, the motion of the peripheral infarct region was calculated as the mean motion of the remaining 50% of the infarct artery territory (Fig. 1). Hyperkinesia was determined from the most hypercontractile 50% of the artery territory opposite the infarct site. Each of these territories has been previously defined as the region of the left ventricle whose motion is depressed by stenosis of the corresponding coronary artery. Ventriculography was performed only in the 30° right anterior oblique projection. However, previous studies (15) have shown that left ventricular volume is more accurately assessed from this projection than from biplane studies, and the severity of hypokinesia in the infarct region is more sensitively detected in the right anterior oblique projection. The only exception is in patients with left circumflex artery thrombosis (16); they were excluded from the present study.

Statistical analysis. Changes in left ventricular function between the acute and the 3 day catheterization were assessed with a paired *t* test. Differences between patients with sustained reperfusion versus no reperfusion or reocclusion

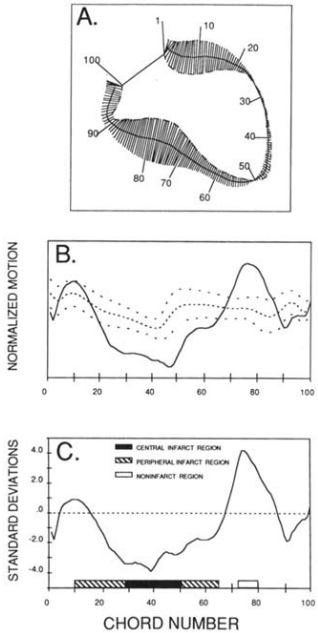

Figure 1. Centerline method of wall motion analysis. **A,** A centerline is constructed midway between the end-diastolic and end-systolic endocardial contours. Motion is measured along 100 chords constructed perpendicular to the centerline. **B,** Motion at each chord is normalized by the end-diastolic perimeter length to yield a shortening fraction. The patient's motion is plotted (**solid line**) in comparison with mean motion ± the SD measured in a normal population (**dashed lines**). **C,** the patient's wall motion is plotted in units of SD from the normal mean (**dashed line**). Wall motion abnormality in the central infarct region, peripheral infarct region and noninfarct region is calculated by averaging the motion of chords lying within these regions. See Methods for region description.

were evaluated with an unpaired *t* test. Differences in left ventricular function among three patient groups (survived, died in hospital, died after discharge) were evaluated with one way analysis of variance. The power of left ventricular function variables in predicting survival was assessed with the Cox regression model and the chi-square test of significance of the regression coefficient. The survival of patients with versus without sustained reperfusion through day 3 was compared using life table analysis.

Results

Patient characteristics (Table 1). The characteristics of the entire study population (n = 226) were similar to those of the group (n = 165) with left ventricular function data for both the acute period and 3 days after myocardial infarction. The 61 patients who lacked paired left ventricular function data were similar to those with complete data in all of these characteristics except that arterial patency in the acute period was achieved somewhat less frequently (77%) ($p = 0.021$).

In 89 patients, data on left ventricular function at 6 months were also available; 76 (85%) had sustained reperfusion and 13 (15%) did not. This subgroup was significantly younger (54 ± 8 versus 57 ± 10 years, $p < 0.01$) and contained a larger proportion of patients with reperfusion, both acutely (92 versus 82%, $p < 0.05$) and through day 3 (85 versus 72%, $p < 0.02$) in comparison with the 137 patients who did not undergo ventriculography three times or whose cine films were not all analyzable.

Effect of reperfusion on left ventricular function (Table 2). The changes in regional wall motion and ejection fraction in patients with and without sustained reperfusion through day 3 are presented in Table 2. There was significant early recovery of left ventricular function in those with thrombosis of the left anterior descending artery (Fig. 2). Surprisingly, motion in the central anterior wall improved to a similar degree in patients with and without sustained reperfusion. However, a great difference was seen in the motion of the peripheral infarct region, which improved slightly in patients with sustained reperfusion but decreased significantly in patients with reocclusion or no reperfusion. As a result, the ejection fraction was maintained at acute levels in those with a patent infarct artery, in significant contrast to the early decrease in ejection fraction in the unsuccessfully treated group.

In the patients with right coronary artery thrombosis, there was no early change in the function of the central infarct region. Motion in the peripheral infarct region tended to improve in patients with sustained reperfusion, and to worsen in those without reperfusion or with reocclusion as in patients with anterior myocardial infarction; but these trends were not statistically significant. Compensatory hyperkinesia in the inferior wall subsided to the same degree in patients with and without sustained reperfusion.

There was a rough but significant correlation between the early change seen in central infarct region function and the acute severity of hypokinesia measured there, in both anterior ($r = 0.35$, $n = 83$, $p < 0.005$) and inferior myocardial infarction ($r = 0.48$, $n = 82$, $p < 0.001$). Function was more likely to increase by day 3 if it was depressed in the acute

JACC Vol. 12, No. 2
August 1988:289–300

Table 1. Characteristics of 226 Patients by Study Group

	All Patients (n = 226)			Patients With Acute and 3 Day LV Data (n = 165)		
	Sustained Reperfusion	No Reperfusion or Reocclusion	p Value	Sustained Reperfusion	No Reperfusion or Reocclusion	p Value
No.	174 (77%)	52 (23%)		134 (81%)	31 (19%)	
Age (yr.)	57 ± 9	54 ± 10	0.061	57 ± 9	53 ± 9	0.025
Gender (% male)	82	88	0.246	83	81	0.773
Infarct artery (% LAD)	60	51	0.283	49	55	0.575
Collateral vessels to infarct artery (%)	11	20	0.061	13	26	0.119
Thrombosis location (% proximal/mid/distal)	49/41/10	46/44/10	0.952	52/38/10	42/45/13	0.792
Time to reperfusion (min)	216 ± 79	205 ± 82 (20)*	0.534	211 ± 76	216 ± 87 (13)	0.834
Acute angioplasty (%)	49	27	0.005	49	32	0.102
Predischarge bypass surgery (%)	21	0	<0.001	19	0	0.016
Acute reperfusion		194 (86%)			147 (89%)	
Reocclusion by day 3		20 (9%)			13 (8%)	

*Parentheses indicate number of patients when < total. LAD = left anterior descending coronary artery; LV = left ventricular.

period to the point of akinesia or dyskinesia. The observed early changes in regional and global left ventricular function were not related to changes in left ventricular end-diastolic pressure or peak systolic pressure ($r < 0.35$ for all) or to administration of nitrates in the acute period.

Examination of left ventricular function in the patients who underwent a third cardiac catheterization at 6 months revealed a significant benefit of reperfusion in those with anterior infarction. Patients with sustained reperfusion had further improvement in the motion of the central infarct region between 3 days and 6 months after infarction and less residual hypokinesia in the peripheral infarct region. As a result, they also had a greater improvement in ejection fraction (5 ± 10%) than did the patients without reperfusion or with reocclusion (−6 ± 12%, $p < 0.02$) (Fig. 3). Patients with inferior myocardial infarction showed similar trends.

Effect of reperfusion on survival (Table 3). In the entire group of 226 patients, long-term survival was significantly ($p < 0.05$) better in those with sustained reperfusion than in those whose infarct artery did not reperfuse or become

Table 2. Left Ventricular Function in 134 Patients With versus 31 Without Sustained Reperfusion on Day 3

	Sustained Reperfusion			Non Reperfusion, Reocclusion or Reinfarction			
	Acute	Day 3	p Value*	Acute	Day 3	p Value*	p Value†
All Patients							
Central IR	−2.8 ± 1.0	−2.6 ± 1.0‡	0.055	−3.2 ± 0.7	−3.1 ± 0.7	0.909	0.429
Peripheral IR	−1.5 ± 1.0	−1.4 ± 1.1‡	0.146	1.6 ± 1.0	−1.9 ± 0.7	0.042	0.025
Non IR	1.3 ± 1.5	0.5 ± 1.4	<0.001	1.1 ± 1.4	0.1 ± 1.5	<0.001	0.335
EF	54 ± 12	52 ± 12‡	0.020	52 ± 13	46 ± 10	<0.001	0.030
No.		134			31		
Anterior myocardial infarction							
Cnetral IR	−2.9 ± 0.8	−2.5 ± 0.9	<0.001	−3.2 ± 0.8	−2.9 ± 0.7	0.046	0.483
Peripheral IR	−1.5 ± 1.0	−1.4 ± 1.2	0.193	−1.4 ± 1.2	−1.9 ± 0.7	0.105	0.048
Non IR	0.8 ± 1.6	−0.0 ± 1.4	<0.001	0.9 ± 1.4	−0.2 ± 1.3	<0.001	0.335
EF	48 ± 12	48 ± 14	0.995	49 ± 14	43 ± 11	0.032	0.036
No.		66			17		
Inferior myocardial infarction							
Central IR	−2.7 ± 1.0	−2.8 ± 1.0‡	0.204	−3.1 ± 0.6	−3.4 ± 0.7	0.073	0.439
Peripheral IR	−1.5 ± 0.9	−1.4 ± 1.0	0.478	−1.7 ± 0.6	−2.0 ± 0.6	0.244	0.275
Non IR	1.7 ± 1.3	1.0 ± 1.1	<0.001	1.3 ± 1.4	0.5 ± 1.6	0.088	0.787
EF	60 ± 10†	56 ± 9‡	<0.001	56 ± 9	56 ± 9	<0.001	0.140
No.		68			14		

*Paired t test, acute versus day 3; †Unpaired t test, comparing the change in function from the acute study to day 3 in patients with sustained reperfusion versus patients with nonreperfusion, reocclusion or reinfarction; ‡left ventricular function measured at this time was significantly ($p < 0.05$) better in the group with sustained reperfusion that in the group with nonreperfusion, reocclusion or reinfarction. EF = ejection; IR = infarct region.

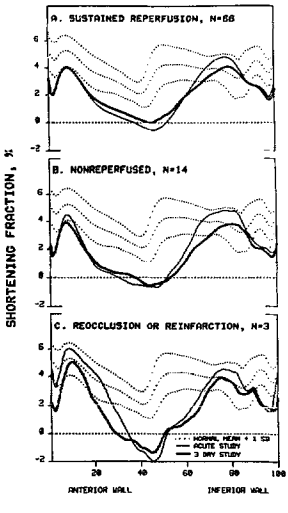

Figure 2. Change in wall motion between the acute study and 3 days after infarction in 83 patients with left anterior descending coronary artery thrombosis. **A,** Motion in patients with sustained reperfusion shows improvement throughout the infarct region. **B,** Patients who do not achieve reperfusion have retraction of apical dyskinesia at 3 days. **C,** All 3 patients who had reocclusion or reinfarction also had retraction of apical dyskinesia, but wall motion decreased along the borders of the infarct region.

reoccluded (Fig. 4). In the study group of 165 patients having paired left ventricular function data (ventriculography on at least two occasions), however, the reperfusion status of the infarct artery did not significantly affect survival (Table 3). This outcome reflects the more frequent omission of ventriculography in patients destined to die early than in those who survived 1 or 2 years ($p < 0.05$).

Effect of left ventricular function on survival (Table 3). Long-term follow-up data were available in 159 (96%) of the 165 patients with both acute and 3 day left ventricular function measurements. Six patients who were lost to follow-up after hospital discharge are included among the survivors, but similar results were obtained if these six were excluded. Five patients (3%) died during the acute hospitalization and 20 (12%) died after discharge. Survivors, who were followed up for 3 to 7 (mean 4.5) years, had significantly better regional and global function on day 3 (Fig. 5).

An additional 11 patients died during hospitalization and therefore did not undergo cardiac catheterization at 3 days. Because the patients who succumbed early had the most depressed left ventricular function, the inclusion of those with missing left ventricular data on day 3 would probably have enhanced rather than diminished the significance of our findings.

The level of left ventricular function measured at 3 days was a more powerful predictor of survival, as indicated by the chi-square value, than was the level measured acutely. This finding was true for the ejection fraction and for wall motion in the central and peripheral infarct regions and the noninfarct region (Table 3). Measurements of left ventricular function made on day 3 were also more predictive of survival than were measurements of the change in function between the acute and 3 day studies, indicating that it is the absolute level of function achieved rather than the magnitude of recovery that determines prognosis.

The global ejection fraction on day 3 not only was the most powerful of the left ventricular function variables in predicting survival, but also correlated more closely with survival than did other clinical variables known to influence prognosis (Table 3). On multivariate analysis, only the ejection fraction on day 3 (chi-square = 23.795, $p < 0.001$) and patient age (chi-square = 7.850, $p = 0.005$) were selected as being significant. Although other variables had demonstrated a significant relation with survival, they were not selected in the multivariate analysis because they correlated significantly with the 3 day ejection fraction and contributed little additional prognostic information. When the acute ejection fraction and history of previous infarction were forced into the Cox regression model, the 3 day ejection fraction continued to step in (chi-square for improvement = 10.671, $p = 0.001$), indicating that the early recovery of the left ventricular function contributes significantly to survival in a manner that is complementary to these other prognostic variables.

Discussion

In the present study, patients with sustained reperfusion had significantly better global left ventricular function 3 days after infarction than did patients whose infarct artery failed to reperfuse or who had reocclusion or reinfarction. Analysis of regional wall motion revealed that in this early period, reperfusion exerted its benefit on function in the peripheral rather than the central infarct region. This action helped to maintain a stable ejection fraction by counterbalancing the decline in compensatory hyperkinesia in the noninfarct region. The level of function achieved by day 3 was a powerful predictor of long-term prognosis, more powerful than left ventricular function in the acute period. These

JACC Vol. 12, No. 2
August 1988:289–300

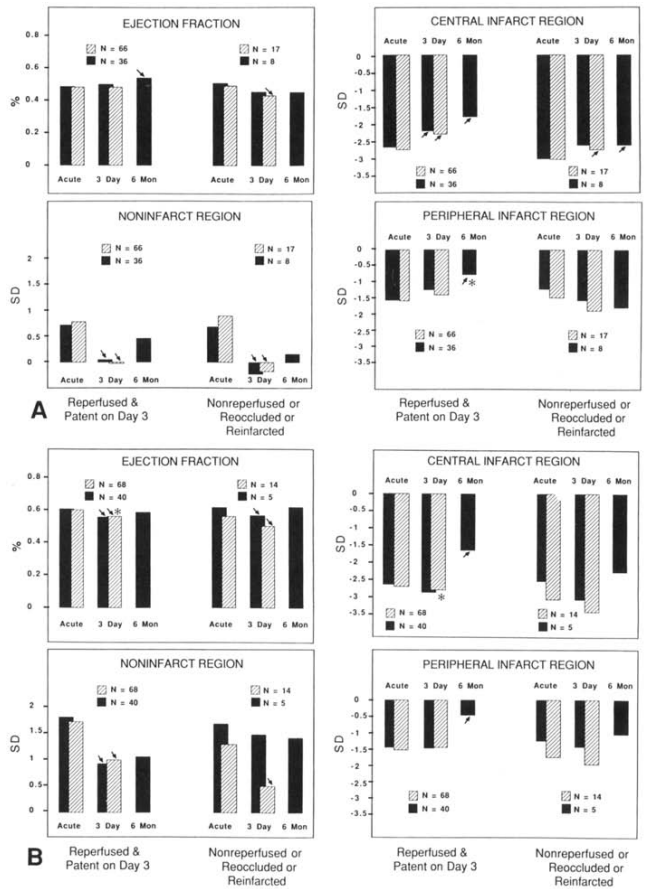

Figure 3. Serial changes in regional and global left ventricular function in patients who underwent contrast ventriculography in the acute period, and at 3 days (n = 165) and 6 months later (n = 89). **A**, Anterior infarction. **B**, Inferior infarction. The improvement measured at 3 days is a fraction of the total recovery seen at 6 months. The changes seen at 3 days are comparable in the groups with (**black bars**) versus those without (**hatched bars**) 6 month data. **Arrows** indicate significant change in left ventricular function from the acute study; **asterisks** indicate that left ventricular function at that time point differs significantly between patients with sustained reperfusion and patients with nonreperfusion, reocclusion or infarction.

Table 3. Univariate Analysis for Variables Predictive of Survival in 165 Patients with Paired Ventricular Function Studies

Variable	Time of Measurement	χ^2	p Value
Ejection fraction	Acute	11.48	0.0007
	3 day	24.59	0.0000
Wall motion			
Noninfarct region	Acute	5.02	0.0251
	3 day	9.18	0.0024
Peripheral infarct region	Acute	1.16	0.2810
	3 day	7.75	0.0054
Central infarct region	Acute	0.36	0.5478
	3 day	1.28	0.2572
Reperfusion status	Acute	0.59	0.4423
	3 day	1.11	0.2911
Age	—	6.13	0.0133
Gender	—	1.12	0.2895
Number of vessels diseased	Acute	0.98	0.3215
Infarct artery (LAD vs. RCA)	Acute	5.51	0.0189
Collateral vessels*	Acute	1.21	0.2708
History of previous infarction		16.32	0.0001

*Collateral vessels to the infarct artery were present acutely in 15% of patients. LAD = left anterior descending coronary artery; RCA = right coronary artery.

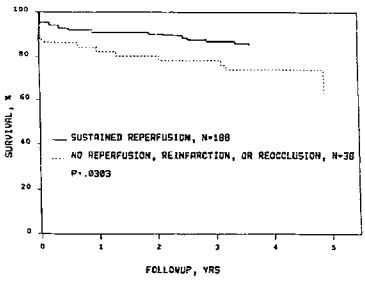

Figure 4. Survival of 188 patients with versus 38 without sustained reperfusion through day 3. Data from the entire group of 226 patients are presented.

findings suggest that thrombolytic therapy enhances survival by maintaining or enhancing left ventricular function in the early days after acute myocardial infarction.

Our observation that the effect of reperfusion on left ventricular function was most evident in patients with anterior infarction is consistent with previous reports (10) showing that survival is improved by thrombolytic therapy only in that subgroup.

Early changes in the function of the "stunned" myocardium. In the present study, function in the central infarct region of patients with anterior myocardial infarction increased significantly between the acute study and day 3. Interpretation of this increase as recovery is probably incorrect, because the same change was seen whether or not sustained reperfusion was achieved. Also, reperfusion after even brief coronary occlusion is not immediately followed by recovery of left ventricular function (17). Instead, there is a delay while the "stunned" myocardium repairs damaged metabolic processes (18,19). It is more likely that anteroapical dyskinesia was reverting to akinesia because of stiffening of the myocardium (20). Early improvement was not seen in the group with inferior infarction, probably because dyskinesia occurs infrequently along the inferior wall. For both walls, the threshold at which early improvement occurred was akinesia; that is, improvement on day 3 was seen in patients whose wall motion was akinetic or dyskinetic in the acute period. Akinesia on the anterior wall represents an abnormality of about 2 SD below normal, but on the inferior wall indicates an unusually severe motion defect that deviates from normal by 3 to 4 SD. Hence, the early improvement in central infarct region function probably reflected decreased compliance rather than recovery. The fact that significant functional recovery was seen at 6 months in patients who achieved reperfusion indicates that the myocardium was not irreversibly damaged at 3 days, but only "stunned."

Mechanisms of early changes in the function of the peripheral infarct region. In the peripheral infarct region, the effect of reperfusion was to prevent deterioration of function. These observations parallel experimental findings. Gibbons et al. (21) reported that the circumferential extent of hypokinesia increased between 30 min and 48 h after permanent coronary occlusion, suggesting that an early worsening in wall motion occurred in the peripheral infarct region. Ellis et al. (22) also reported that contractile function in the peripheral ischemic zone worsened between 90 min and 6 h in dogs subjected to permanent coronary occlusion, whereas function began to recover within these early hours in dogs undergoing reperfusion.

Early deterioration in function in the peripheral infarct region may be due to withdrawal of endogenous catecholamine activity, to which the decline in hyperkinesia in the noninfarct region has been attributed. An argument against this mechanism is the lack of correlation ($r < 0.20$) between changes in the peripheral infarct and noninfarct regions. However, it may be an oversimplification to expect sympathetic activity to affect motion in these two regions equally because the peripheral infarct region is tethered to and therefore influenced by motion changes in the central infarct region (23,24). A second mechanism that may explain the deterioration in peripheral infarct region function in patients without sustained reperfusion is expansion or extension, or both, of the infarct (25). Reocclusion or clinical reinfarction,

JACC Vol. 12, No. 2
August 1988:289-300

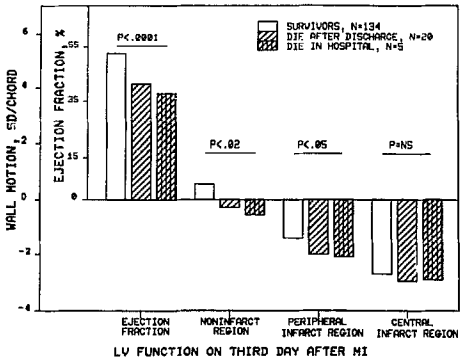

Figure 5. Regional (wall motion) and global (ejection fraction) left ventricular (LV) function measured 3 days after myocardial infarction (MI) in 134 patients who survived a mean of 4.5 years, 20 who died after hospital discharge and 5 who died during the initial hospitalization; p values indicate significance as assessed using one way analysis of variance.

or both, occurred in 3 of the 17 patients with anterior infarction and 10 of the 14 with inferior infarction in the present study, which may have contributed to the declining function in this region. Third, left ventricular dilation may artifactually reduce the calculated fractional shortening in the absence of true change in endocardial excursion. Dilation is not uncommon in anterior myocardial infarction but would be unusual in a first inferior infarction (26), and only 7% of our patients with inferior infarction had had a previous infarction. Although this finding could not be ruled out in the present study because of the lack of calibration, an excessive increase in volume would be required to yield the observed decrease in regional function (see Appendix).

Regardless of the mechanism, the significance of these early changes in function in the peripheral infarct region derives from their contribution to the global ejection fraction. At 3 days, when the central infarct region remains severely depressed, it is the recovery in the peripheral infarct region that mediates the effect of reperfusion on the ejection fraction.

Clinical studies of the time course of changes in left ventricular function. Studies (27–30) in patients not treated with thrombolytic agents have failed to demonstrate any consistent changes in left ventricular function in the first few days after acute myocardial infarction. For example, Wackers et al. (28) measured the ejection fraction serially and reported spontaneous changes that exceeded the variability in ejection fraction observed in patients in stable condition, but did not correlate with hemodynamic status. However, all of these studies utilized radionuclide rather than contrast ventriculography, which limited their ability to analyze regional wall motion, and the studies were on patients who did not receive thrombolytic therapy and in whom the patency of the infarct artery was unknown. Therefore, the decline in global function observed in our patients 3 days after myocardial infarction may have been obscured in these earlier studies by the spontaneous improvement seen in patients with subendocardial infarction (31) or with subtotal occlusion (32). Such patients constitute 15 to 20% of patients with acute infarction presenting with ≥2 mm ST segment elevation on the admission ECG (32,33) and were excluded from the present study to reduce variability.

Several clinical studies (34–36) have also compared function measured before versus immediately after successful thrombolytic therapy. With one exception (34), these studies found no acute recovery in either regional or global function, although significant recovery was observed before discharge. These data indicate that the immediate post-reperfusion measurements in these studies were performed when and where the myocardium was still "stunned" (18).

Thus, the failure of previous studies to observe the early changes in regional and global left ventricular function noted in our patients can be attributed to differences in patient population, imaging techniques and timing of ventriculography. However, our findings are concordant with experimental data showing that reperfusion can result in early recovery of left ventricular function, particularly in regions bordering the zone of deepest ischemia.

Relations among reperfusion, left ventricular function and prognosis. Regardless of whether it is measured shortly after admission, in the course of intracoronary thrombolytic therapy (37), 24 h after admission (38) or before discharge (39–41), the ejection fraction has consistently proven to be one of the strongest predictors of mortality. The present study adds

confirmation to these earlier studies. Furthermore, our data show that the ejection fraction measured 3 days after infarction is so powerful a predictor of mortality that the acute ejection fraction fails to add significantly to a discriminant function and is rejected in multivariate analysis.

These results indicate that the change in ejection fraction over the first 3 hospital days is an important determinant of subsequent survival. Because patients who achieved sustained reperfusion had a higher 3 day ejection fraction than did unsuccessfully treated patients, our data suggest that thrombolytic therapy enhances survival by improving left ventricular function in the early postinfarction period. The observation that reperfusion protected wall motion in the peripheral infarct region in the early days after acute infarction does not contradict the concept of the "stunned" myocardium, but rather is consistent with reports that functional recovery is more rapid in border regions (22,42,43).

The possibility cannot be ruled out from the present data that thrombolytic therapy may also enhance survival by improving left ventricular function in other regions at other times. For example, reperfusion may accelerate functional recovery in the central infarct region, because experimental studies (42) have shown that both the magnitude and the rate of recovery are greater in reperfused than in nonreperfused ischemic myocardium. Additional studies with more frequent measurements of left ventricular function are needed to further define the effects of reperfusion.

Survival after myocardial infarction is also influenced by other factors such as the patient's age, gender, history of angina, hypertension, previous infarction or arrhythmias or by concordant therapy such as revascularization or beta-adrenergic blocking agents. Some of these are, of course, unalterable. Others, such as the arrhythmias, reflect the patency of the infarct vessel or the magnitude of ischemia. In the present study, data on these clinical variables were not available for correlation with survival. However, concordant therapy may enhance survival in one or more ways by increasing perfusion, preventing reocclusion, and reducing infarct size or improving ventricular function.

In our previous studies (44), surgery performed during the acute hospitalization period was associated with better survival, which we attributed to maintenance of the beneficial effect of reperfusion. In the present study, two thirds of the coronary bypass operations were performed after the 3 day ventriculogram and may have similarly maintained the beneficial effect of reperfusion on left ventricular function that was seen on day 3.

Function in the noninfarct region. In several recent controlled trials (8,45,46), streptokinase therapy resulted in enhanced function in the noninfarct region, particularly in patients with multivessel disease or anterior infarction. In contrast, reperfusion status did not significantly affect function in the noninfarct region in the early postinfarction period in past or present nonplacebo-controlled studies (47). A possible mechanism for this paradox may be that streptokinase enhances global perfusion by reducing blood viscosity (48). This action may reduce ischemic dysfunction in the noninfarct region directly or by facilitating collateral flow to the infarct region, or both (49). Regardless, it is well known that wall motion abnormalities in the noninfarct region affect global left ventricular function (50–52). By correlating the level of function in this region with survival (Table 3), the present data confirm the importance of the noninfarct region and its ability to compensate for the dysfunction of the infarct region.

Implications of measuring left ventricular function versus infarct size. In the present analysis, we evaluated the effect of thrombolytic therapy on left ventricular function rather than on infarct size. Although myocardial salvage achieved by reperfusion is often expressed in terms of left ventricular function, salvage is defined anatomically as a reduction in the mass of infarcted myocardium from that anticipated if no intervention is applied (53). Under controlled conditions infarct size and left ventricular function correlate highly, but the relation varies with the duration of coronary occlusion, the patency of the infarct artery and the time at which function is measured (54–56). These factors increase variability in the assessment of infarct size and salvage from ventricular function measurements in humans. Therefore, no attempt was made to extrapolate, from the functional data, the degree of salvage achieved or its relation to survival. Indeed, measurements of infarct size and of early recovery of function may yield disparate results in studies of therapeutic interventions for acute myocardial infarction. For example, treatment with the xanthine oxidase inhibitor oxypurinol enhanced early recovery of left ventricular function in dogs did not reduce infarct size (57). In another experimental study (54), reperfusion after a 2 h coronary occlusion resulted in greater recovery of left ventricular function than did reperfusion after a 4 h occlusion, but infarct size was the same in both groups.

Clinical implications. The present data show that reperfusion achieved with intracoronary streptokinase therapy enhanced long-term survival and resulted in a significant early benefit to wall motion in the peripheral infarct region and to global left ventricular function, and that the resultant level of ventricular function measured at 3 days was more predictive of survival than was that measured immediately after thrombolysis. These findings suggest that the mechanism by which thrombolytic therapy enhances survival is improvement of regional and global left ventricular function early after acute myocardial infarction. Consequently, because the majority of deaths attributable to acute myocardial infarction do occur within the first few days, future studies of therapeutic interventions should examine the effect of treatment on early functional recovery.

JACC Vol. 12, No. 2
August 1988:289–300

Appendix

The following exercise is an estimate of the magnitude of left ventricular dilation required to yield the observed decrease in wall motion noted in the infarct region in patients with reocclusion or without reperfusion between the acute and 3 day cardiac catheterizations. For the purpose of discussion, the dimensions of the left ventricle in the study at the time of acute infarction are assumed to equal the values observed in our normal reference population of 52 subjects, who underwent diagnostic cardiac catheterization and were found to have normal cardiac anatomy. In wall motion analysis by the centerline method, the percent shortening fraction (SF) at each of the 100 chords is calculated as:

$$SF = \frac{100 \times M}{EDP}, \quad (1)$$

where M = motion of chord i during systole (centimeters) and EDP = end-diastolic perimeter length (centimeters).

1. Anterior infarction. In the normal population, the standard deviation for motion in the territory of the left anterior descending coronary artery which spans chords 10 to 66 as previously defined (13), averages 1.17%, and the mean end-diastolic perimeter is 25.8 cm. In the 17 patients with anterior myocardial infarction without reperfusion or with reocclusion, function in the peripheral infarct region decreased by 0.5 SD from an acute mean shortening fraction of 1.98% (1.4 SD below the normal shortening fraction in the anterior wall, 3.62%). Substituting into (1) yields absolute chord motion (M) in the left anterior descending coronary artery territory:

$$1.98 = \frac{100 \times M}{25.8},$$

then M = 0.51 cm.

Assume that chord motion remains unchanged, and that the decrease in shortening fraction (that is, 0.5 SD × 1.17%/SD) seen on day 3 is caused by left ventricular dilation, which increases the end-diastolic perimeter by a factor I:

$$1.98 - (0.5 \times 1.17) = \frac{100 \times 0.51}{25.8 \times I},$$

then I = 1.42, a 42% increase in perimeter.

The circumference (C) of an ellipse is calculated as:

$$C = 2\pi \sqrt{\frac{a^2 + b^2}{2}} \cong 4.443 \sqrt{a^2 + b^2}. \quad (2)$$

To estimate the dimensions of the left ventricle associated with a 42% increase in end-diastolic perimeter length, the ratio of the minor to major axis a/b will be set to 0.68, the value observed in patients with diffuse hypokinesia due to coronary artery disease (58). Although the left ventricular contour in the 30° right anterior oblique projection resembles an ellipse, the end-diastolic perimeter length of a left ventricle is longer than the circumference of an ellipse of equal area and long-axis length due to the irregularities of the left ventricular contour. In our normal population, the circumference of the equivalent ellipse is 91% of the actual perimeter length. Substituting in equation (2):

$$25.8 \times 0.91 = 4.443 \sqrt{(0.68b)^2 + b^2},$$

then b = 4.37 cm and a = 2.97 cm.

With the area-length method, volume is calculated as:

$$V_{calc} = \frac{4}{3} \pi a^2 b = 161 \text{ ml}. \quad (3)$$

A regression equation is then applied to the calculated volume (V_{calc}) to correct for overestimation due to the inclusion of volume occupied by papillary muscles and trabeculae carneae (12):

$$V = V_{calc} \times 0.81 + 1.9, \quad (4)$$

then V = 133 ml.

If the perimeter length increases by 42%, then a and b increase by 42% and volume by a factor of $(1.42)^3$ or 2.86. Thus nearly a tripling of volume is required to cause the shortening fraction in the peripheral anterior wall to deteriorate by the observed amount, 0.5 SD, if the actual extent of systolic motion remains constant.

2. Inferior infarction. A similar analysis in the inferior wall results in the following findings: The normal SD in the right coronary artery territory, chords 51 to 80, averages 1.15%. In the 14 patients without sustained reperfusion, motion in the central infarct region declined by 0.35 SD from an acute mean shortening fraction of 2.13% (1.7 SD below the normal shortening fraction in the inferior wall, 4.08%).

$$2.13 = \frac{100 \times M}{25.8}, \; M = 0.55 \text{ cm} \quad (1)$$

$$2.13 - (0.35 \times 1.15) = \frac{100 \times 0.55}{25.8 \times I},$$

then I = 1.23, a 23% increase in perimeter length. Thus, left ventricular volume must increase by $(123)^3$ or 1.86, that is, nearly double to yield the observed decrease in shortening fraction, if there is no change in the magnitude of systolic wall motion.

Because these magnitudes of left ventricular dilation exceed values previously reported in patients after acute myocardial infarction who did not undergo thrombolytic therapy (59), the early deterioration of function in the peripheral infarct region in the present study cannot be attributed to an increase in left ventricular chamber volume.

References

1. Verani MS, Roberts R. Preservation of cardiac function by coronary thrombolysis during acute myocardial infarction: fact or myth? J Am Coll Cardiol 1987;10:470–6.
2. Gruppo Italiano per lo studio dello streptochi-nasi nell'infarto miocardico. Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report on the GISSI study. Lancet 1987;2:871–4.
3. Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. N Engl J Med 1983;309:1477–82.
4. Ritchie JL, David KB, Williams DL, Caldwell J, Kennedy JW. Global and regional left ventricular function and tomographic radionuclide perfusion: the Western Washington Intracoronary Streptokinase in Myocardial Infarction Trial. Circulation 1984;70:867–75.
5. Kennedy JW, Martin GV, Davis KB, et al. The Western Washington Intravenous Streptokinase in Acute Myocardial Infarction Randomized Trial. Circulation 1988;77:345–52.
6. The I.S.A.M. Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (ISAM): mortality, morbidity, and infarct size at 21 days. N Engl J Med 1986;314:1465–71.
7. Simoons ML, van de Brand M, de Zwaan C, et al. Improved survival after early thrombolysis in acute myocardial infarction, a randomized trial by the Interuniversity Cardiology Institute in the Netherlands. Lancet 1985;2:578–82.

8. Serruys PW, Simoons ML, Suryapranata H, et al. Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction. J Am Coll Cardiol 1986;7:729–42.

9. White HD, Norris RM, Brown MA, et al. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. N Engl J Med 1987;317:850–5.

10. Kennedy JW, Ritchie JL, Davis KB, Stadius ML, Maynard C, Fritz JK. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction: a 12-month follow-up report. N Engl J Med 1985;312:1073–8.

11. Sievers J. Myocardial infarction: clinical features and outcome in three thousand thirty-six cases. Acta Med Scand 1964;175(406):1–123.

12. Dodge HT, Sandler H, Ballew DW, Lord JD, Jr. The use of biplane angiocardiography for the measurement of left ventricular volume in man. Am Heart J 1960;60:762–76.

13. Sheehan FH, Bolson EL, Dodge HT, Mathey DG, Schofer J, Woo HW. Advantages and applications of the centerline method for characterizing regional ventricular function. Circulation 1986;74:293–305.

14. Sheehan FH, Dodge HT, Mathey DG, Brown BG, Bolson EL, Mitten S. Application of the centerline method: analysis of change in regional left ventricular wall motion in serial studies. In: Computers in Cardiology. Long Beach: IEEE Computer Society, 1982:97–100.

15. Wynne J, Green LH, Mann T, Levin D, Grossman W. Estimation of left ventricular volumes in man from biplane cineangiograms filmed in oblique projections. Am J Cardiol 1978;41:726–32.

16. Sheehan FH, Schofer J, Mathey DG, et al. Measurement of regional wall motion from biplane contrast ventriculograms: a comparison of the 30 degree RAO and 60 degree LAO projections in patients with acute myocardial infarction. Circulation 1986;74:796–804.

17. Heyndrickx GR, Millard RW, McRitchie RJ, Maroko PR, Vatner SF. Regional myocardial functional and electrophysiological alterations after brief coronary artery occlusion in conscious dogs. J Clin Invest 1975;56:978–85.

18. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982;66:1146–9.

19. Jennings RB and Steenbergen JR. Nucleotide metabolism and cellular damage in myocardial ischemia. Ann Rev Physiol 1985;47:727–49.

20. Hood WB, Bianco J, Kumar R, Whiting RB. Experimental myocardial infarction. IV. Reduction of left ventricular compliance in the healing phase. J Clin Invest 1970;49:1316–23.

21. Gibbons EF, Hogan RD, Franklin TD, Nolting M, Weyman AE. The natural history of regional dysfunction in a canine preparation of chronic infarction. Circulation 1985;71:394–402.

22. Ellis SG, Henschke CI, Sandor T, Wynne J, Braunwald E, Kloner RA. Time course of functional and biochemical recovery of myocardium salvaged by reperfusion. J Am Coll Cardiol 1983;1:1047–55.

23. Wyatt HL, Forrester JS, da Luz PL, Diamond GA, Chagrasulis R, Swan HJC. Functional abnormalities in nonoccluded regions of myocardium after experimental coronary occlusion. Am J Cardiol 1976;37:366–72.

24. Kerber RE, Marcus ML, Ehrhardt J, et al. Correlation between echocardiographically demonstrated segmental dyskinesis and regional myocardial perfusion. Circulation 1975;52:1097–104.

25. Hutchins GM, Bulkley BH. Infarct expansion versus extension: two different complications of acute myocardial infarction. Am J Cardiol 1978;41:1127–32.

26. Eaton LW, Weiss JL, Bulkley BH, Garrison JB, Weisfeldt ML. Regional cardiac dilatation after acute myocardial infarction. N Engl J Med 1979;300:57–62.

27. Schelbert HR, Henning H, Ashburn WL, Verba JW, Kartiner JS, O'Rourke RA. Serial measurements of left ventricular ejection fraction by radionuclide angiography early and late after myocardial infarction. Am J Cardiol 1976;38:407–15.

28. Wackers FJ, Berger HJ, Weinberg MA, Zaret BL. Spontaneous changes in left ventricular function over the first 24 hours of acute myocardial infarction: implications for evaluating early therapeutic interventions. Circulation 1982;66:748–54.

29. Ramanathan K, Bodenheimer MM, Banka VS, Helfant RH. Natural history of contractile abnormalities after acute myocardial infarction in man: severity and response to nitroglycerin in man. Circulation 1981;63:731–8.

30. Reduto LA, Berger HJ, Cohen LS, Gottschalk A, Zaret BL. Sequential radionuclide assessment of left and right ventricular performance after acute transmural myocardial infarction. Ann Intern Med 1978;89:441–7.

31. Dawson JR, Sutton GC. Incoordinate left ventricular wall motion after acute myocardial infarction. Br Heart J 1984;51:545–2.

32. Leiboff RH, Katz RJ, Wasserman AG, et al. A randomized, angiographically controlled trial of intracoronary streptokinase in acute myocardial infarction. Am J Cardiol 1984;53:404–7.

33. Sheehan FH, Mathey DG, Schofer J, Dodge HT, Bolson EL. Factors determining recovery of left ventricular function following thrombolysis in acute myocardial infarction. Circulation 1985;71:1121–8.

34. Rentrop P, Blanke H, Karsch KR. Changes in left ventricular function after intracoronary streptokinase infusion in clinically evolving myocardial infarction. Am Heart J 1981;102:1188–93.

35. Charuzi Y, Beeder C, Marshall LA, et al. Improvement in regional and global left ventricular function after intracoronary thrombolysis: assessment with two-dimensional echocardiography. Am J Cardiol 1984;53:662–5.

36. Reduto LA, Smalling RW, Freund GC, Gould KL. Intracoronary infusion of streptokinase in patients with acute myocardial infarction: effects of reperfusion on left ventricular performance. Am J Cardiol 1981;48:403–9.

37. Stadius ML, Davis K, Maynard C, Ritchie JL, Kennedy JW. Risk stratification for 1 year survival based on characteristics identified in the early hours of acute myocardial infarction: the Western Washington Intracoronary Streptokinase Trial. Circulation 1986;74:703–11.

38. Shah PK, Pichler M, Berman DS, Singh BN, Swan HJC. Left ventricular ejection fraction determined by radionuclide ventriculography in early stages of first transmural myocardial infarction. Am J Cardiol 1980;45:542–6.

39. Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med 1983;309:321–36.

40. Schulze RA Jr, Strauss HW, Pitt B. Sudden death in the year following myocardial infarction. Am J Med 1977;62:192–8.

41. Borer JS, Rosing DR, Miller RH, et al. Natural history of left ventricular function during 1 year after acute myocardial infarction: comparison with clinical, electrocardiographic and biochemical determinations. Am J Cardiol 1980;46:1–12.

42. Lavallee M, Cox D, Patrick TA, Vatner SF. Salvage of myocardial function by coronary artery reperfusion 1, 2, and 3 hours after occlusion in conscious dogs. Circ Res 1983;53:235–47.

43. Roan PG, Buja M, Izquierdo C, Hashimi H, Shaffer S, Willerson JT. Interrelationships between regional left ventricular function, coronary blood flow, and myocelfular necrosis during the initial 24 hours and 1 week after experimental coronary occlusion in awake, unsedated dogs. Circ Res 1981;49:31–40.

44. Mathey DG, Schofer J, Sheehan FH, et al. Improved survival up to 4 years after early coronary thrombolysis. Am J Cardiol 1988;61:524–9.

45. Martin GV, Sheehan FH, Stadius M, et al. Intravenous streptokinase for acute myocardial infarction: effects on global and regional systolic function. Circulation (in press) 1988.

46. Bassand JP, Faivre R, Becque O, et al. Effects of early high-dose streptokinase intravenously on left ventricular function in acute myocardial infarction. Am J Cardiol 1987;60:435–9.

47. Sheehan FH, Mathey DG, Schofer J, Krebber HJ, Dodge HT. Effect of interventions in salvaging left ventricular function in acute myocardial infarction: a study of intracoronary streptokinase. Am J Cardiol 1983;52:431–8.

JACC Vol. 12, No. 2
August 1988:289–300

48. Theiss W, Volger E, Wirtzfeld A, Keisel I, Blomer H. Gerinnungsbefunde und rheologische Messungen bei Streptokinasebehandlung des akuten Myokardinfarktes. Klin Wschr 1980;58:607–15.

49. Gascho JA, Lesnefsky EJ, Mahanes MS, Kaiser DL, Beller GA. Effects of acute left anterior descending occlusion on regional myocardial blood flow and wall thickening in the presence of a circumflex stenosis in dogs. Am J Cardiol 1984;54:399–406.

50. Hood WB. Experimental myocardial infarction. III. Recovery of left ventricular function in the healing phase. Contribution of increased fiber shortening in noninfarcted myocardium. Am Heart J 1970;79:531–8.

51. Widimsky P, Gregor P, Cervenka V, Visek V. Two-dimensional echocardiography in acute transmural and non-transmural myocardial infarction. Cor Vasa 1984;26:12–9.

52. Sheehan FH, Szente A, Mathey DG, Dodge HT. Assessment of left ventricular function in acute myocardial infarction: the relationship between global ejection fraction and regional wall motion. Eur Heart J 1985;6(suppl. E):117–25.

53. Reimer KA. Myocardial infarct size. Arch Pathol Lab Med 1980;104:225–30.

54. Bush LR, Buja LM, Samowitz W, et al. Recovery of left ventricular segmental function after long-term reperfusion following temporary coronary occlusion in conscious dogs. Circ Res 1983;53:248–63.

55. Falsetti HL, Marcus ML, Kerber RE, Skorton DJ. Quantification of myocardial ischemia and infarction by left ventricular imaging. Circulation 1981;63:747–51.

56. Hammerman H, O'Boyle JE, Cohen C, Kloner RA, Parisi AF. Dissociation between two-dimensional echocardiographic left ventricular wall motion and myocardial salvage in early experimental acute myocardial infarction in dogs. Am J Cardiol 1984;54:875–9.

57. Puett DW, Forman MB, Cates CU, et al. Oxypurinol limits myocardial stunning but does not reduce infarct size after reperfusion. Circulation 1987;76:678–86.

58. Gould KL, Lipscomb K, Hamilton GW, Kennedy JW. Relation of left ventricular shape, function and wall stress in man. Am J Cardiol 1974; 34:627–34.

59. Nieminen M, Heikkila J. Echoventriculography in acute myocardial infarction II: monitoring of left ventricular performance. Br Heart J 1976;38:271–81.